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Acute pancreatitis: a comparison of intervention rates precipitated by early vs guideline CT scan timing --Manuscript Draft--

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Abstract:	<p>AIM To assess whether CT scanning earlier in acute pancreatitis (AP) precipitates any surgical or radiological intervention.</p> <p>MATERIALS AND METHODS A single centre retrospective cohort study comparing intervention rates in AP precipitated by early (<6 day of admission, n=100) and UK guideline (≥6 day of admission, n=103) CT scans.</p> <p>RESULTS No intervention was precipitated by scanning before the 6th day of admission in AP. A statistically significant larger number of interventions were precipitated when scanning on the 6th day or later (P<0.05). Of note this study was conducted using day of admission, rather than day of symptom onset. 6 patients underwent repeat scanning in the same admission after an early scan.</p> <p>CONCLUSION Scanning before the 6th day of admission does not lead to earlier intervention. Such early scans waste resources and may offer false reassurance to clinicians.</p>

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Acute pancreatitis: a comparison of intervention rates precipitated by early vs guideline CT scan timing

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8. Manuscript editing: Ian Zealley, Sarah Vinnicombe

ABSTRACT

AIM

To assess whether CT scanning earlier in acute pancreatitis (AP) precipitates any surgical or radiological intervention.

MATERIALS AND METHODS

A single centre retrospective cohort study comparing intervention rates in AP precipitated by early (<6 day of admission, n=100) and UK guideline (≥ 6 day of admission, n=103) CT scans.

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No intervention was precipitated by scanning before the 6th day of admission in AP. A statistically significant larger number of interventions were precipitated when scanning on the 6th day or later ($P<0.05$). Of note this study was conducted using day of admission, rather than day of symptom onset. 6 patients underwent repeat scanning in the same admission after an early scan.

CONCLUSION

Scanning before the 6th day of admission does not lead to earlier intervention. Such early scans waste resources and may offer false reassurance to clinicians.

Acute pancreatitis: a comparison of intervention rates precipitated by early vs guideline CT scan timing

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ABSTRACT

AIM: To assess whether computed tomography (CT) examination earlier in acute pancreatitis (AP) precipitates any surgical or radiological intervention.

MATERIALS AND METHODS: A single-centre retrospective cohort study comparing intervention rates in AP precipitated by early (<6 day of admission, $n=100$) and UK guideline (≥ 6 day of admission, $n=103$) CT examinations.

RESULTS: No intervention was precipitated by performing CT before the sixth day of admission in AP. A statistically significant larger number of interventions were precipitated when CT was performed on the sixth day or later ($p<0.05$). Of note, this study was conducted using day of admission, rather than day of symptom onset. Six patients underwent repeat CT examination in the same admission after an early CT examination.

CONCLUSION: Performing CT before the sixth day of admission does not lead to earlier intervention. Such early examinations waste resources and may offer false reassurance to clinicians.

INTRODUCTION

Computed tomography (CT) is the workhorse investigation for the identification and classification of complications of acute pancreatitis (AP) [1]. In 2005, the UK Working Party on Acute Pancreatitis issued guidelines for the management of patients with AP [2]. These have not been superseded and remain current for UK practice. The guidelines suggest that CT be performed only for patients with persisting organ failure, signs of sepsis, or clinical deterioration 6–10 days after admission [2]. More recent guidelines from the American College of Gastroenterology differ in detail, but in essence support the UK recommendation [3]. This selective approach to CT in AP is based on two principles: first, that the initial management of AP is entirely supportive [2,4]. Radiological and surgical interventions during the later stages of AP are only performed for symptomatic complications, such as infected pancreatic necrosis, with interventions only indicated in patients whose clinical condition is not improving with supportive management[2]. Second, that it has been demonstrated that CT undertaken "too early" can underestimate both the presence and extent of pancreatic necrosis [1,2,5,6].

The early phase of AP (within the first 6 days) is characterised by a systemic inflammatory response [3,7], which may cause substantial physiological deterioration leading to understandable clinical concern. Anecdotally, in Ninewells Hospital and elsewhere, this concern may precipitate "too early" (<6 days) CT being requested and performed. The usual justification for "too early" CT is a desire to improve

outcome through early intervention. It is also sometimes asserted that the timing of initial CT should more appropriately be from symptom onset, not admission date as the guidelines state.

In order to determine whether or not "too early" CT does, in fact, lead to therapeutically useful interventions in patients with AP the present study was undertaken to determine (1) the frequency of CT examinations performed at <6 days and at ≥6 days, and (2) the frequency of surgical and radiological interventions precipitated by CT findings in these groups.

MATERIALS AND METHODS

Patients and groups

This single-centre retrospective cohort study was performed under approval from the local Caldicott Guardian. No patient identifiable information is presented. The setting was a 995-bed teaching hospital serving a population of approximately 400,000. The study was designed to test the null hypothesis that intervention rates precipitated by CT are not significantly different in those scanned ≥6 days after admission, compared to those scanned before 6 days.

A computerised search of the radiological information system (RIS) and hospital information system (HIS) was undertaken employing the following inclusion criteria: clinical information (1) includes the word "pancreatitis", (2) inpatient, (3) serum amylase on admission >100. For each patient, the following data were recorded from HIS and RIS: age; sex; days elapsed since admission to scan; amylase level; reason for scan, including if there were other differentials; diagnosis from scan, including any complications; any radiological intervention for complications of pancreatitis; and any surgical intervention for complications of pancreatitis.

The start date selected for the search was 10 June 2010. This was the date on which a radiology department memorandum was circulated reminding radiologists about the content of the UK guideline. The memorandum summarised the recommendation relating to appropriate timing of CT examinations and was intended to aid appropriate vetting of requests for CT in patients with AP. The RIS and HIS search continued until the number of cases in both groups met the planned sample size.

A further RIS and HIS search was undertaken to identify therapeutic procedures (radiological and surgical) performed in relation to complications of AP, which had been identified at CT.

Cases were categorised into four groups as follows: (1) CT scan performed at ≥ 6 days, firm clinical/biochemical diagnosis of AP, scan performed to assess for complications of AP; (2a) CT scan performed at < 6 days, firm clinical/biochemical diagnosis of AP, no diagnostic uncertainty, no clinically important additional diagnosis entertained; (2b) CT scan performed at < 6 days, clinical/biochemical diagnostic uncertainty (equivocal amylase 100–999), to assess for evidence of pancreatitis in order to establish diagnosis; (2c) CT scan performed at < 6 days, suspected or confirmed AP, but an additional clinically important differential diagnosis is entertained (e.g., perforation of hollow viscus).

Statistical analysis

As there were no prior data available regarding the intervention frequencies, the findings for the initial 20 cases were used to perform a statistical power calculation. These initial data demonstrated a 10% incidence of intervention in the group scanned ≥ 6 days after admission, with 0% intervention rate for patients scanned before day 6. From this, it was calculated that 142 patients, with 71 patients scanned

at ≥ 6 days and 71 scanned at < 6 days, were required to have an 80% likelihood of detecting a decrease in the primary outcome measure from 10% in the guideline group to 0% in the early group with a 5% level of statistical significance for the difference. Consequently, the aim was to accrue 100 cases for each category as a pragmatic target sample size to allow for incomplete datasets.

Categorical variables were summarised by frequency and percentage. The difference between intervention rates in the two groups was analysed using Fisher's exact test.

RESULTS

The RIS and HIS search of sequential cases fulfilling the inclusion criteria was continued until the planned total of at least 100 episodes of "too early" (< 6 days). The date of the final accrued case was 27 October 2013. Sequential selection resulted in 103 "within guideline" scans being included once 100 early scans had been accrued. The demographics for each patient group are shown in Table 1.

Table 2 tabulates the breakdown of scan category into each of the four groups described, with the number of interventions and frequency with which the CT scan changed diagnosis. Fifty-six of the 159 patients (35%) with a firm clinical/biochemical diagnosis of AP had "too early" CT examinations performed before the UK guideline recommendations. Twenty-four patients underwent more than one CT examination during their admission; six of these patients had a firm clinical/biochemical diagnosis of AP and underwent "too early" (< 6 days) CT examinations, with later repeat CT examinations performed to assess for complications of AP once again.

No radiological or surgical intervention (0/100) was precipitated in the "too early" CT group (< 6 days after admission). Conversely a 15% (15/103) intervention rate was

observed in the guideline (≥ 6 days) group ($p=0.000036$). Excluding early CT examinations performed for equivocal amylase or to identify suspected additional diagnoses, the difference remains statistically significant, with 0/56 interventions in the early group compared to 15/103 interventions in the later group ($p=0.0013$). Post hoc power calculation of this second comparison shows it is powered to $>90\%$ with the same significance level. On this basis, the null hypothesis can confidently be rejected, and it is clear that intervention rates precipitated by CT are significantly different in those scanned ≥ 6 days after admission, compared to those scanned before 6 days. Furthermore, in the present study no intervention was precipitated by early CT.

DISCUSSION

When there is a firm clinical/biochemical diagnosis of pancreatitis, no alternate diagnoses are demonstrated and no therapeutic interventions are precipitated by undertaking CT before the sixth day of admission. This illustrates the futility of early scanning, and adds significant clinical weight in support of adherence to the UK Working Party Guidelines [2], including the notion of 6 days from admission, not symptom onset.

Further evidence of the importance of waiting until Day 6 of admission is the finding that six patients in the early group underwent at least one further CT examination at a later date in the same admission to assess for complications of AP. Such duplicated CT examinations exposes patients to unnecessary radiation and intravenous contrast medium. Although studies have shown no short-term morbidity from early CT [8], the cumulative stochastic effects of the radiation remain. The

present finding that no interventions are precipitated as the result of early CT is consistent with findings of a lack of morbidity and mortality

Although nearly 10-years old, the 2005 UK Working Party guidelines remain current and have not been superseded in the UK [2]. They underpin the Clinical Knowledge Summary published by the National Institute for Health and Care Excellence (NICE) in 2010 [4], and are formed from a multidisciplinary working group including both clinical and radiological staff. Like the UK Working Party guidelines, the updated Atlanta classification of terminology related to AP, which is not itself a management guideline, suggests that CT "when necessary" be performed at 5–7 days after admission [9].

Another guideline relating to the management of AP was published by the American College of Gastroenterology (ACG) in 2013 [3], which suggests, "Contrast-enhanced computed tomography (CECT) and/or magnetic resonance imaging (MRI) of the pancreas should be reserved for patients in whom the diagnosis is unclear or who fail to improve clinically within the first 48–72 hours after hospital admission (strong recommendation, low quality of evidence)" [3]; however, a review of the papers used to support this statement shows that (1) sterile collections do not require intervention, (2) early intervention in infected necrosis is associated with increased mortality and should be postponed until at least 30 days if possible, and (3) drainage through any method is optimal when a collection is given time to become walled off.[1,10–13] The early scanning recommendation is also made in the diagnosis section, as opposed to the assessment section of the UK Working Party guidelines and the Atlanta classification.[2,9] This subtle shift in emphasis may explain the earlier imaging recommendation.

It should be noted that data collection for the volume of early scans required was only possible due to poor adherence to the guidelines. What is unclear is whether this is due to vetting radiologists being unfamiliar with the guidelines or pressure from clinicians due to clinical concern. This study offers reassurance to both clinicians and radiologists that no chance to intervene early will be missed by waiting until 6 days after admission, and should reinforce adherence to the guideline.

There are disadvantages inherent in the retrospective study design employed. It is possible that some sampling bias and misclassification bias may have been introduced, but steps were taken to minimise these risks [14]. The start date for the study was not based on any change in practice or work patterns in the surgical service and was not influenced by any assumptions regarding variation or changes in clinical practice. Consecutive cases that fulfilled predetermined inclusion criteria were selected. The inclusion criteria were defined fairly broadly, in a manner intended to maximise the likelihood that all appropriate patients would be captured and included in the study. The four categories into which patients were allocated were defined as strictly as possible in order to minimise the possibility of misclassification of individual patients. Overall the study was designed in a fashion that was adapted to limitations of retrospective data collection. Data fields were clearly defined, but were broad enough to capture all relevant patients over the period of study, and the use of robust electronic RIS and HIS data sources ensured maximum data capture.

A further issue that arose during the execution of this study, and which occurs in clinical practice generally, is determining the time of onset of AP itself. Although most patients present within a few hours of onset, there are some who present several days into the course of the disease. Determining whether or not the timing of CT is

optimised for these patients is a challenge. The argument is often made that the time elapsed from symptom onset should be used as opposed to admission date. For the purposes of this study, the strict wording of the UK Working Party guideline was adhered to, which recommends the time period of, "...6–10 days after admission..." [2]. Finally, the intervention rate is the only outcome measured in this study. Although it may have been interesting to look at overall morbidity and mortality, other studies that address this already exist [8].

On the other hand, there are some advantages to the retrospective study design employed. Firstly, the requesting physicians and the vetting radiologists could not be influenced by awareness that their practice was being evaluated. This eliminated the possibility of observation bias, which a prospective study design would necessarily invoke. The number of events studied confers a degree of validity to the results, which would be difficult to replicate with a prospective study design. Another benefit is that the study was conducted over an extended period, reducing the effect of any short-term variations in practice.

In summary, CT examinations performed before the sixth day of admission precipitated no interventions. The difference in intervention frequencies precipitated by early versus late scanning is confirmed without statistical doubt by this study. Furthermore, these findings are with strict adherence to the wording of the guideline, with the first day of admission being used as the start point for timing [2]. This study adds clinical evidence to the existing scientific basis of the UK Working Party on Acute Pancreatitis guideline [2], as well as raising doubt over the earlier imaging suggested in the American College of Gastroenterology guideline[3]. It offers support to the vetting radiologist considering the appropriateness of CT timing in acute pancreatitis. Finally, it may reassure clinicians that despite the often severe nature of

acute pancreatitis, no benefit is gained from undertaken CT before the sixth day of admission.

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Table 1. Patient demographics

	CT timing		
	<6 days	≥6 days	Overall
Scans	100	103	203
Male	71	62	103
Female	29	41	70
Median age	57	60	58
Age range	20-85	20-88	20-88

Table 2. Summary of management changes based on CT scan findings, by scan category

	No. of CT examinations	Times diagnosis altered	Intervention frequency
Day 6 or later, firm diagnosis	103	0	15
Before day 6, firm diagnosis	56	0	0
Before day 6, equivocal diagnosis	22	2	0
Before day 6, alternate differential	22	4	0

HIGHLIGHTS

- Zero intervention rate in early scanning adds clinical support to the existing guidelines regarding CT in acute pancreatitis.
- After early scanning, patients often require repeat scans in the same admission.
- Avoiding early CT scanning in acute pancreatitis saves resources without impacting on patient care